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EXAMINER	
LEFFERS JR,G	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/439,969	Applicant(s) Madhani, Hiten
	Examiner Gerald G. Leffers Jr.	Group Art Unit 1636

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-18* is/are pending in the application.

Of the above, claim(s) *1-8, 14, and 16-18* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *9-13 and 15* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-4, 14 and 16-18, drawn to methods of inhibiting invasion of a host by a fungus by inhibiting expression of a gene in the filamentous MAPK pathway, classified in class 514, subclasses 1, 2, 44; class 424, subclass 130.1.

II. Claims 5-8, drawn to a method of inhibiting invasion of a host by a fungus by inhibiting the activity of a gene product encoded by a member of the filamentous MAPK pathway, classified in class 514, subclasses 1, 2; class 424, subclass 130.1.

III. Claims 9-13 and 15, drawn to methods of identifying inhibitors of gene expression for members of the MAPK signal transduction pathway, classified in class 435, subclasses 6, 29.

The inventions are distinct, each from the other because of the following reasons:

Inventions of Groups I-III are biologically and functionally different and distinct from each other and thus one does not render the other obvious. The methods of Groups I-III comprise steps which are not required for or present in the methods of the other groups: contacting the fungus with a compound which inhibits expression of a gene expressed in the filamentation MAPK pathway (Group I), contacting the fungus with a compound which inhibits the activity of a gene product encoded by a gene expressed in the filamentation MAPK pathway (Group II) and

providing an expression vector comprising a nucleic acid molecule encoding a gene which is expressed in the filamentation MAPK pathway (Group III). The end results of the methods from the different groups are different: inhibition of invasion of a host by a fungus through interfering with expression of gene expressed in the filamentation MAPK pathway (Group I), inhibition of invasion of a host by a fungus by interfering with the activity of a gene product encoded by a gene expressed in the filamentation MAPK pathway (Group II) and identification of a compound that inhibits expression of a gene expressed in the MAPK pathway (Group III). Thus, the operation, function and effects of these different methods are different and distinct from each other. Therefore, the inventions of the different, distinct groups are capable of supporting separate patents.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, and because the non-patent literature search required for Group I (e.g. antisense- and ribozyme-mediated inhibition of gene expression) is not required for Group II, restriction for examination purposes as indicated is proper.

During a telephone conversation with Doreen Hogle on or about 6/7/00 a provisional election was made with traverse to prosecute the invention of Group I, claims 9-13 and 15. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-8, 14 and 16-18 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, predictability of the art, state of the prior art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The nature of the invention is extremely complex, involving the identification of inhibitors of a complicated Kss1 MAPK-dependent signal transduction/developmental pathway in yeast by expression from a vector of a gene normally expressed as part of the pathway in the presence or absence of a test compound and determining if expression of the gene is repressed by the test compound. The complexity of the invention is exacerbated by the stipulation within the claims that the simple determination the presence of the test compound decreases transcription of

the Kss1 MAPK-regulated gene means the test compound necessarily inhibits the developmental pathway and by the breadth of the claims which encompass any genes expressed in the pathway.

The guidance given by the specification is minimal. The term "filamentation MAPK pathway" is ill defined in the specification. The specification teaches that the Kss1 MAPK pathway is involved in two related developmental processes for yeast: haploid invasive growth in response to a nutrient rich environment and filamentous growth as a diploid in response to nitrogen starvation characterized by dramatic cell elongation not seen in haploids. It is unclear, however, whether the term "filamentation MAPK pathway" encompasses only those genes expressed in the haploid invasive growth phase, genes only expressed during the diploid filamentous growth phase or any gene expressed as part of the Kss1 MAPK pathway. The specification teaches that one can determine if a gene is expressed in the "filamentation MAPK pathway" if it is 1) identified as having repressed expression in the presence of galacturonic acid (the product of pectin digestion by the secreted pectinase PGU1), 2) identified as being expressed in haploid fungal cells and not expressed in diploid fungal cells or 3) identified as being repressed by Tec1 expression (page 9, lines 23-28). Yet the data given in the specification for genes involved in the pathway are contradictory. All of the genes identified by applicant as "regulated by the filamentation MAPK pathway" appear to be stimulated for expression, rather than repressed, by the expression of TEC1 from a high copy plasmid in haploid cells grown in nutrient-rich media (Figure 1). Of these genes which are expressed in the Kss1 MAPK pathway,

only YELO33W demonstrates repression in response to the presence of galacturonic acid as well as preferential expression in haploid cells.

The specification also does not provide a definition of what constitutes "inhibition" of the filamentous MAPK pathway, merely stating that inhibition of gene expression for one of the members of the pathway constitutes inhibition of the pathway. There is no guidance or suggested assay from the specification for how one would determine if the "filamentation" pathway has in fact been inhibited by the presence of a test agent, other than the observation that the expression of one of the genes of the pathway has been inhibited. It is not clear from reading the specification as to what the endpoint of the pathway actually is, which would be a logical point for designing such an assay to quantitatively or qualitatively measure inhibition of the pathway. In fact, there is very little guidance for the relationship between the different members of the Kss1 MAPK pathway beyond what little was already known in the art (e.g. Figure 11). There is almost no guidance for the relationship amongst the newly discovered, putative members of this pathway beyond a suggestion of a feedback mechanism for the regulation of YELO33W, a gene apparently regulated by the Tec1-STE12 transcription factor specific to the filamentation pathway, by one of the digestion products generated by an enzyme (PGU1) which is also apparently part of the pathway. The function that YELO33W has within the pathway or outside of the pathway is apparently unknown.

There are no working examples in the specification in which the effects of a test agent on the filamentation pathway are assessed other than expression profile assays for putative members

of the pathway in response to the presence of polygalacturonic acid (pectin) or galacturonic acid. There is no attempt in any of these assays to correlate the increase or decrease in expression of any of the pathway genes in response to the test agents to an actual effect on the pathway itself. The only data presented within the specification with regard to the effects of a lack of transcription for any of the putative members of the filamentation pathway are gene knockout data in which no functional copy of the gene is present. Of the 18 genes described by applicants as regulated by the filamentation MAPK pathway, only one (FLO11) was shown to be required for either haploid invasive growth or for diploid filamentation (Figure 3). Knockout of one other gene, YELO33W, was shown to affect both haploid invasive growth and diploid filamentation. The absence of expression for any of the other putative filamentation pathway genes did not appear to significantly affect either haploid growth or diploid filamentation.

The state of the art in understanding the different components and interactions of the Kss1 MAPK pathway is not very high. As taught by Madhani et al "Despite their recognized function in driving development in diverse organisms, little is known about how signaling leads to observed changes in cellular behavior." (page 12530, column 1). Madhani et al present much of the same data presented in the instant application regarding the identification of putative members of the Kss1 MAPK pathway. With regard to the knockout data in which no effect was seen for several putative members of the Kss1 MAPK pathway, Madhani et al teach "Surprisingly, of nine gene knockouts tested....only one (corresponding to YELO33W) had an obvious defect in haploid invasion and pseudohyphal development. The lack of an invasion

defect in the other eight knockout strains could result from (i) a function in a coregulated process not measured in the laboratory invasion assay or (ii) a function in invasive growth that is redundant with that of another gene." (page 12531, column 2). Madhani et al argue that the first hypothesis is supported by the observation that the activity of the secreted pectinase, PGU1, is apparently absolutely dependent on the Kss1 MAPK pathway and that the role PGU1 plays in the normal host-saprophyte ecology of S.cerevisiae is that of a facilitator for invasive growth of fruit (which has pectin as a major structural component of the barriers to invasion such as the peel) (page 12532, columns 1-2). Madhani et al suggest that the role of PGU1 as a target of the filamentation pathway is not as a promoter of filament formation per se, but as an enzymatic attacker of the plant host. Thus, the state of the art teaches that it is not readily predictable whether a decrease in the expression of a particular gene of the Kss1 MAPK pathway will affect the pathway itself, of if it does whether one will necessarily detect the effect because of the possibility that the effect is not directly on filament formation or that the activity of the product encoded by the gene itself is redundant.

Given the lack of guidance within the specification as to what genes are actually expressed in the "filamentation MAPK pathway", the lack of guidance as to what would constitute "inhibition" of the pathway beyond a decrease in gene expression for one of the putative members of the pathway, the breadth of the claims which encompass any gene "expressed in the filamentation pathway", the lack of guidance with regard to what would be an appropriate assay for measuring inhibition of the pathway or even what end-point of the pathway

would be appropriate for developing such an assay, the complete lack of working examples in which a test agent was applied to growing cells in order to measure its effect on the pathway, the minimal guidance regarding the role of any of the putative MAPK pathway genes in the pathway or their relationship with one another and the lack of predictability as taught by the instant application, or in the art by Madhani et al, regarding the effects of no transcription, much less merely "inhibited" transcription, for any of the genes encompassed by the claims on either haploid invasive growth or diploid filamentation, it would require undue, unpredictable experimentation to make and use even one embodiment of applicant's claimed invention.

One of skill in the art would have to determine if a particular gene is expressed as part of the "filamentous MAPK pathway", envision an appropriate assay to determine the effects of its transcriptional repression on the pathway, clone the gene into a "suitable" vector for expression in a "suitable" host cell, express the gene in the presence or absence of a test agent, determine if expression of the gene is inhibited by the presence of the test agent and, if such an effect on expression is observed, perform the envisioned assay for detecting the effects of repressed transcription of the particular gene on the "filamentous MAPK pathway" and determine if the test agent inhibited the pathway. If unsuccessful, which is likely given the teachings of the instant application and Madhani et al that it is unpredictable whether even the complete lack of expression for the vast majority of the pathway genes will demonstrate a detectable effect on the pathway, one of skill in the art will then have to decide whether the lack of an observed effect on the pathway was due to the degree of inhibition of expression of the particular pathway gene,

whether the pathway gene is still considered a good target for such an inhibitor or whether the assay was an appropriate assay for that particular pathway gene. One of skill in the art would then either have to envision another gene and/or assay combination which might be appropriate for screening compounds that will inhibit the "filamentation MAPK pathway" by inhibiting expression of the envisioned pathway gene, repeat the process of expressing the gene in the host cell in the presence or absence of a test agent and determine if the test agent inhibits expression of the envisioned gene. If the test agent did inhibit the expression of the envisioned gene, one would then have to perform the same assay, or another different one, to determine whether the test agent also inhibited the filamentation pathway. If it did not, which is again likely given the teachings of the instant specification and Mahdani et al, one of skill in the art would have to repeat the entire process until successful. Thus, it would take undue, unpredictable experimentation to make and use even one embodiment of the claimed invention. Therefore, the claimed invention of a method of identifying an agent which inhibits the filamentation MAPK pathway in a fungus by inhibiting the expression of a member of that pathway is not considered to be enabled by the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-13 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to claims 9 and 15, the term "providing" in a separate step implies the step has patentable weight when in fact it is a trivial step and does not add to the claim. Amending the claims to delete the term "providing" and combining the "providing" step with the next step would be remedial.

Claim 9 is vague and indefinite in that the metes and bounds of the term "..comprising a nucleic acid molecule of a gene which is expressed..." are unclear. From the context provided by the rest of the claim and from reading the specification it appears that the term is meant to specify an expression vector comprising a nucleic acid encoding a protein whose gene is expressed as part of the "filamentation MAPK pathway". It would be remedial to amend the claim language to clearly indicate that the expression vector comprises a nucleic acid sequence encoding a functional protein.

Claim 9 is vague and indefinite in that the metes and bounds of the term "inhibits the filamentation MAPK pathway" are not clear on at least two grounds. This term does not appear to be well defined in the specification. The specification teaches that the Kss1 MAPK pathway is involved in two related developmental events, haploid invasive growth on rich media and diploid pseudohyphal development (i.e. conversion of a diploid cells to greatly elongated cells which are not seen with the haploids). It is unclear from reading the entire specification as to whether the

term "filamentation MAPK pathway" refers to 1) the genes expressed during haploid growth in response to rich media, 2) the genes expressed during diploid growth in response to nitrogen starvation to form elongated cells, or 3) any genes expressed by diploid or haploid cells which are regulated by the Tec1-STE12 transcription factor which is taught to be specific to the Kss1 MAPK pathway. It would be remedial to amend the claim language to clearly indicate which of the genes regulated by the Kss1 MAPK pathway are encompassed by the term "filamentation MAPK pathway"

The term "inhibits the filamentation MAPK pathway" of claim 9 is also unclear in that the claim language and the specification do not define the criteria by which one determines the pathway has been inhibited, making it unclear as the claim is written as to whether there is a missing step in the method of claim 9. Does inhibition of the expression of any one of the genes expressed during the "filamentation MAPK pathway" necessarily constitute an inhibition of the pathway itself or is there a missing step where the degree of pathway inhibition is determined by the effect of the inhibition of gene expression on the endpoint of the pathway? For example, if the endpoint of the pathway is the ability to form diploid, elongated filaments then does the ability to grow under conditions which induce diploid filamentation (e.g. the ability of a PGU1 knockout to grow under the such conditions as shown in Figure 3) mean that the pathway is not inhibited? It would be remedial to amend the claim to clearly indicate any additional step or criteria needed to determine whether the pathway has been inhibited by the test agent.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers, Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

GLJr

G. Leffers, Jr.

Patent Examiner

Art Unit 1636

June 30, 2000

TERRY MCKELVEY
PRIMARY EXAMINER